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Description

This invention relates to the use of phenyl quinoline carboxylic acids and derivatives thereof for preparing pharmaceutical compositions for treating skin and muco-epithelial diseases.

5 U.S. Patent 4,680,299, granted July 14, 1987, to Hesson describes phenyl quinoline carboxylic acids and their derivatives as tumor inhibiting agents. Antitumor agents are typically administered internally by injection or by an oral dosage form.

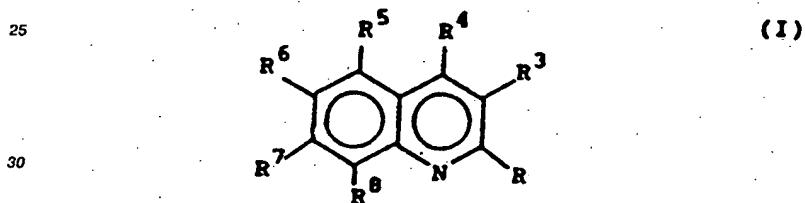
10 Many diseases of the skin and muco-epithelia, such as psoriasis, are characterized by an inflammatory reaction in the underlying connective tissue and a hyperplasia (increased mitotic activity) of the overlying epithelia. Agents which suppress either or both the inflammatory and mitotic activity of the epithelia are effective in treating diseases of the skin.

15 The current treatment for skin and muco-epithelial diseases (i.e. psoriasis and chronic dermatitis) is primarily based upon topical steroids. These are efficacious but have significant side effects such as skin atrophy, rosacea and adrenal suppression and thus are limited in their chronic usage.

20 A second common treatment for psoriasis is the use of coal tar or its derivatives. This treatment is unpleasant, not very effective and has potential for carcinogenesis. For moderate to severe cases of psoriasis, psoralens with UVA or drugs such as methotrexate or cyclosporin A, whose side effects are kidney failure or liver toxicity, have been used with success.

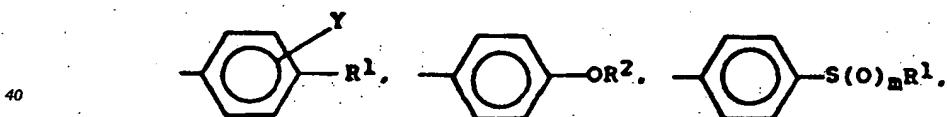
25 No treatment is presently available which is at the same time effective, safe and cosmetically acceptable. Hence, a need exists for better treatment of skin and muco-epithelial diseases. The compounds described in U.S. Patent 4,680,299 may offer improved efficacy over steroid and anti-metabolite therapy.

20 According to the present invention there is provided the use of a compound having the formula:

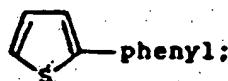


wherein

35 R is

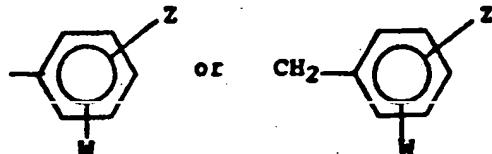


45 or



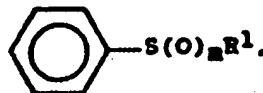
50 R1 is $\text{CH}_3\text{CH}_2(\text{CH}_3)\text{CH}_2$, alkyl of 5-12 carbon atoms, cyclohexyl,

5



10 when R is

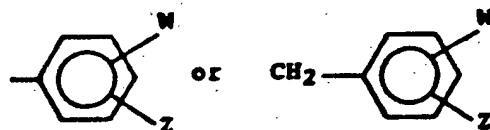
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R^1
 R^2
 can be in addition alkyl of 3-4 carbon atoms;
 is



30

 R^3

is H, alkoxy of 1-3 carbon atoms, or alkyl of 1-2 carbon atoms;
 R^4 is CO_2H or CO_2R^{11} ;

R^5 , R^6 , R^7 and R^8 are independently H, F, Cl, Br, I, CH_3 , CF_3 , SCH_3 or CH_2CH_3 , at least two of R^5 , R^6 , R^7 and R^8 being H;

R^9 and R^{9A} are independently H or alkyl of 1 to 3 carbon atoms;
 R^{11} is $(CH_2)_2-4.NR^9R^{9A}$;

35

 W and Z

m are independently H, F, Cl, Br, alkyl of 1-5 carbon atoms, NO_2 , OH, CF_3 or OCH_3 ;
 m is 0 or 1; or

a pharmaceutically suitable salt thereof;
 with the following provisos:

(1) R^5 , R^6 and R^7 cannot all be H;

40

(2) when R^4 is $CO_2CH_2CH_2N(CH_3)_2$, R^6 is CH_2CH_3 , or R^7 is Cl, R^1 cannot be cyclohexyl;

(3) when R^1 is cyclohexyl and R^3 is H, R^6 must be Cl or F, but R^6 and R^8 cannot both be Cl; and

(4) when R^6 is CH_3 , then R^7 cannot be Cl,

for the preparation of a medicament for the treatment of a skin or muco-epithelial disease in a mammal.

45

Also provided is a pharmaceutical composition adapted for topical administration, to the exclusion of internal administration, comprising a carrier suitable for topical formulation and an efficacious amount of one of the aforesaid compounds.

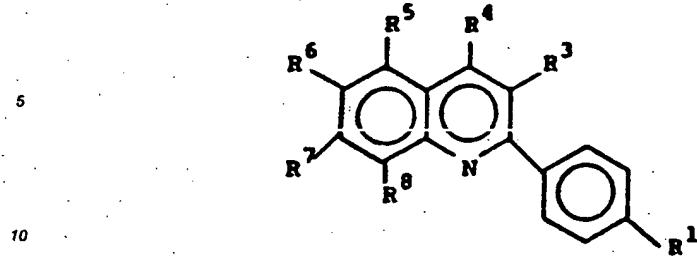
Additionally provided is the above-described use and topical composition wherein the above-described compound is administered in combination with a steroid drug.

Preferred compounds useful in the present invention have the formula:

50

55

(II)



wherein

R¹is cyclohexyl; phenyl; phenyl substituted with one halogen, alkyl of 1-5 carbon atoms or CF₃; phenoxy; or phenoxy substituted with one halogen or alkyl of 1-5 carbon atoms;R³

is H or alkyl of 1-2 carbon atoms;

R⁴is CO₂H, a sodium or potassium salt thereof; or CO₂R¹¹;R⁵ and R⁶are independently H, halogen, CH₃ or CF₃;R⁷ and R⁸

are independently H or halogen;

R¹¹is (CH₂)₂₋₄NR⁹R^{9A}; andR⁹ and R^{9A}

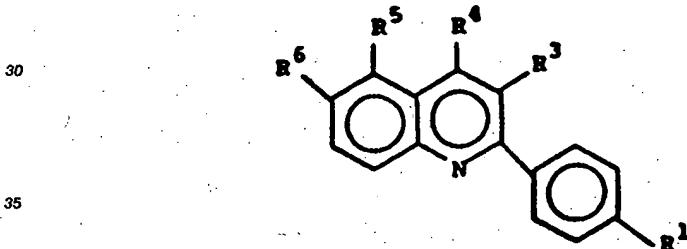
are independently alkyl of 1 to 3 carbon atoms,

or a pharmaceutically suitable salt thereof;

provided that R⁵, R⁶ and R⁷ cannot all be H and that when R¹ is cyclohexyl and R³ is H, R⁶ must be Cl or F, but R⁶ and R⁸ cannot both be Cl, and when R⁶ is CH₃, then R⁷ cannot be Cl.

More preferred compounds useful in this invention have the formula:

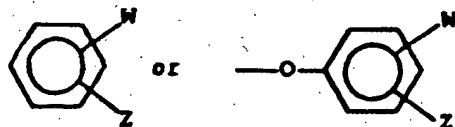
(III)



wherein

R¹

is cyclohexyl,

R³

is H or alkyl of 1-2 carbon atoms;

R⁴is CO₂H, a sodium or potassium salt thereof, or CO₂R¹¹;R⁵ and R⁶are independently H, halogen or CF₃ provided that both R⁵ and R⁶ are not hydrogen;R¹¹is (CH₂)₂₋₄NR⁹R^{9A}; andR⁹ and R^{9A}

are independently alkyl of 1 to 3 carbon atoms; and

W and Z

are independently H, halogen, alkyl of 1-5 carbon atoms or CF₃;provided that when R¹ is phenyl or phenoxy, and R⁵ is H, then R⁶ cannot be Br; and that when R¹ is cyclohexyl and R³ is H, R⁶ must be Cl or F.

Specifically preferred compounds useful in this invention are:

(1) 2-(1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinoline carboxylic acid, sodium or potassium salt

(2) 6-fluoro-3-methyl-2-(4-phenoxyphenyl)-4-quinoline carboxylic acid, sodium or potassium salt
 (3) 2-(4'-bromo-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinoline carboxylic acid, sodium or potassium salt
 (4) 2-(2'-fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinoline carboxylic acid, sodium or potassium salt
 (5) 2-(1,1'-biphenyl-4-yl)-5-chloro-3-methyl-4-quinoline carboxylic acid, sodium or potassium salt.

5 The compounds useful in this invention are described in and prepared by methods set forth in U.S. Patent 4,680,299.

The invention can be further understood by the following examples in which parts and percentages are by weight unless otherwise indicated; all temperatures are in degrees centigrade.

10 Example 1

Part A: 2-(1,1'-Biphenyl-4-yl)-5-chloro-3-methyl-quinoline-4-carboxylic acid

15 A mixture of 4-chloroisatin (7.28 g, .04 mol), [J. Am. Chem. Soc., 1251 (1956)], 4-phenylpropiophenone (8.8 g, .04 mol), diethylamine (4 ml, .04 mol) and ethanol (200 ml) was stirred for a period of 18 hours at room temperature. The precipitated solids were collected by filtration, washed with ice-cold ethanol and air dried to yield the adduct (9.1 g, 58%) m.p. 209-214° C.

20 Part B:

The above described adduct (9.1 g) was added to a mixture of tetrahydrofuran (200 ml), and concentrated HCl (200 ml) and heated at reflux for 24 hr. The reaction mixture was cooled, water (300 ml) was added and most of the tetrahydrofuran removed by evaporation in vacuo. The aqueous residue was cooled and the sticky solids collected by filtration. Trituration in 150 ml of boiling methanol yielded (4.8 g, 55%) m.p. 295-297° C.

$C_{23}H_{16}ClNO_2$ HRMS: 373.0869 Calcd, measured m/e 373.0814.
 1H NMR (DMSO- d_6): δ 8.5(m,1H), 7.7-7.85(m,7H), 7.35-7.55(m,4H), 2.45(s,3H).

30 Part C: Sodium 2-(1,1'-Biphenyl-4-yl)-5-chloro-3-methyl-quinoline-4-carboxylate

To a suspension of the above acid (3.7 g, .01 mol) in ethanol 100 ml, sodium hydroxide (1N, 10 ml, .01 mol) was added, and gently warmed. The clear solution was then filtered and evaporated to dryness to yield (4.0 g) m.p. 320-330° C.

35 Example 2

Part A: 2-(2-Fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinoline carboxylic acid

40 5-Fluoroisatin (72.6 g, 0.44 mol) and 4-(2-fluorophenyl)propiophenone (100 g, 0.44 mole) were suspended in 720 ml of ethanol and stirred mechanically as a solution of KOH (147.8 g, 2.64 mol) in 300 ml of water was added dropwise over 15 minutes. The reaction mixture was heated at reflux for 12 hours, cooled and the ethanol evaporated under reduced pressure. The resulting solid was dissolved in water and washed with ethyl ether. The aqueous layer was cooled to 5° C and acidified with glacial acetic acid. The resulting precipitate was filtered, washed 2 times with 300 ml of ethyl ether and dried. Recrystallization from dimethylformamide and water gave 84 g of a white 2-(2'-Fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinoline carboxylic acid, m.p. 315°-317° C.

50 Part B: Sodium 2-(2'-Fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methylquinoline-4-carboxylate

The compound of Part A (37.5 g, 0.10 mol) was suspended in 1,000 ml of ethanol and treated with 1N NaOH (100 ml, 0.10 mol). The mixture was warmed and stirred until clear; the ethanol and water were evaporated at reduced pressure to give 39.6 g of the white solid sodium 2-(2'-fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methylquinoline-4-carboxylate, m.p. >360° C.

55 Results of the biological tests described below establish that the compounds useful in this invention have the ability to inhibit skin hyperplasia induced by the repeated application of tetradecanoyl phorbol acetate (TPA) to mouse ears (Marks, et al., Cancer Res., 36:2636, 1976). As described, TPA is known to induce changes in murine skin which mimics many of the inflammatory and epithelial changes which occur

in human skin diseases such as psoriasis.

TPA-Induced Hyperproliferation

5 CF-1 male mice (Charles River; weight:20-25 g) were treated orally with compound prepared in 0.25% Methocel® (Dow Chemical Co.) one hour prior to the application of 1 µg of TPA (in acetone) to the right ear with acetone only to the left ear. This treatment was repeated once a day for a total of 4 consecutive days. On day 5, the animals were injected intraperitoneally with 2 mg/kg of vinblastine sulfate to arrest dividing cells in metaphase. Four hours later, the animals were sacrificed and the ears removed for histological processing. The histological slides were then examined in a light microscope and the metaphase figure per millimeter basement membrane counted. Ten mice were used per group. Results are shown in Tables 1 and 2.

TABLE 1

Group	Dose (mg/kg)	TPA	Mitotic Activity Metaphase/mm BM* ± SEM** Figures
Negative Control	-	-	1.3 ± 0.3
Positive Control	-	+	16.2 ± 1.1
Methotrexate	10.0	-	1.0 ± 0.2
	10.0	+	9.0 ± 1.1
Example 1	10.0	-	1.2 ± 0.4
	10.0	+	5.1 ± 0.4
Example 2	10.0	-	1.4 ± 0.2
	10.0	+	8.4 ± 1.3

* mm BM = millimeters of basement membrane

** SEM = standard error of mean

30 The test results show that the compounds described herein effectively suppress the mitotic activity associated with mouse skin hyperplasia induced by TPA, indicative of efficacy in treating human skin and muco-epithelial diseases such as psoriasis (in all its forms), lichen planus, chronic eczema, ichthyosis, pityriasis and chronic urticaria.

35 The phenylquinolinecarboxylic acid derivatives useful in this invention can be administered to treat skin and muco-epithelial diseases such as psoriasis (in all its forms), lichen planus, chronic eczema, ichthyosis, pityriasis and chronic urticaria. These compounds may be administered by any means that produces contact of the active agent with the agent's site of action in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents, e.g., in combination with steroid drugs, particularly topical steroids such as Synalar (fluocinolone acetonide), Lidex (fluocinolone), Westcort (hydrocortisone valerate), Valisone (betamethasone valerate), and Diprasone (betamethasone dipropionate). They can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

40 The dosage administered will, of course, vary depending upon known factors such as the pharmacodynamic characteristics of the particular agent, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms; kind of concurrent treatment, frequency of treatment, and the effect desired. Usually a daily dosage of active ingredient can be 0.1 to 100 milligrams per kilogram of body weight. Ordinarily 0.5 to 50, and preferably 1 to 10 milligrams per kilogram per day given in divided doses 1 to 6 times a day or in sustained release form is effective to obtain desired results.

45 Dosage forms (compositions) suitable for internal administration contain from about 1 milligram to 500 milligrams of active ingredient per unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of 0.5 - 95% by weight based on the total weight of the composition.

50 The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. It can also be administered parenterally, in sterile liquid dosage forms, by inhalation in the form of a nasal spray or lung inhaler, or topically as an ointment, cream or lotion.

55 Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, sucrose, mannitol,

starch, cellulose derivatives, magnesium stearate and stearic acid. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

5 Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions.

10 Solutions for parenteral administration contain the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid either alone or combined are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl or propyl-paraben, and chlorobutanol.

15 Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, A. Osol, a standard reference text in this field.

Useful pharmaceutical dosage forms for administration of the compound useful in this invention can be illustrated as follows:

20 Capsules

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 50 milligrams of powdered active ingredient, 175 milligrams of lactose, 24 milligrams of talc, and 6 milligrams of magnesium stearate.

25 Soft Gelatin Capsules

A mixture of active ingredient in soybean oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 50 milligrams of the active ingredient. The capsules are washed in petroleum ether and dried.

30 Tablets

35 A large number of tablets are prepared by conventional procedures so that the dosage unit is 50 milligrams of active ingredient, 6 milligrams of magnesium stearate, 70 milligrams of microcrystalline cellulose, 11 milligrams of cornstarch and 225 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

38 Injectable

40 A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is sterilized by commonly used techniques.

45 Suspension

An aqueous suspension is prepared for oral administration so that each 5 milliliters contain 25 milligrams of finely divided active ingredient, 200 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin.

50 Nasal Spray

An aqueous solution is prepared such that each 1 milliliter contains 10 milligrams of active ingredient, 1.8 milligrams methylparaben, 0.2 milligrams propylparaben and 10 milligrams methylcellulose. The solution is dispensed into 1 milliliter vials.

55 Lung Inhaler

A homogeneous mixture of the active ingredient in polysorbate 80 is prepared such that the final concentration of the active ingredient will be 10 milligrams per container and the final concentration of polysorbate 80 in the container will be 1% by weight. The mixture is dispensed into each can, the valves are crimped onto the can and the required amount of dichlorotetrafluoroethane is added under pressure.

5

Topical Formulations

An ointment for topical administration is prepared at 70°C by adding the active ingredient to a mixture of 48% by weight white petrolatum, 10% liquid petrolatum, 8% glycerol monostearate, 3% isopropyl myristate and 20% lanolin. After thorough mixing, a warm solution of methyl and propyl parabens in water containing sodium acetone bisulfite is added such that the final concentrations of each paraben is 0.15%, of water is 8% and of sodium acetone bisulfite is 0.5%. The mixture is stirred until it has reached room temperature.

A cream for topical administration is prepared at 75°C by adding the active ingredient to a mixture of 1% sodium lauryl sulfate, 12% propylene glycol, 25% stearyl alcohol, 25% white petrolatum and 37% water. The mixture is stirred until it congeals.

A gel for topical administration is prepared at 70°C by adding the active ingredient to a mixture of 0.75% Carbopol 940 (polycarbopol), 46.25% water, 3% emulsifier hydroxylated lanolin, 50% ethanol and, optionally, 1-2% diisopropanolamine. The mixture is stirred until it cools to room temperature.

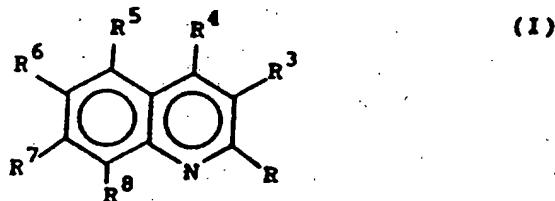
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Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

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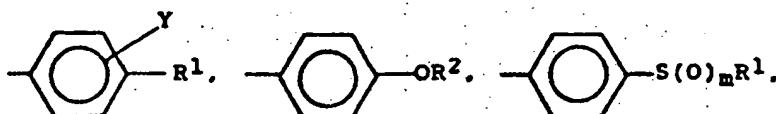
1. Use of compounds having the formula:



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wherein
R is

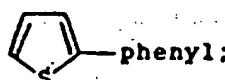
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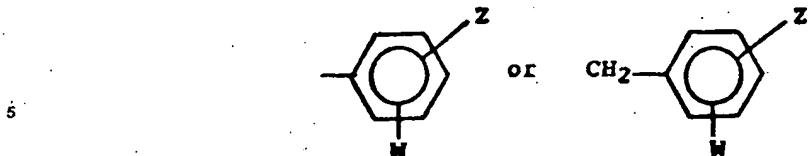
or

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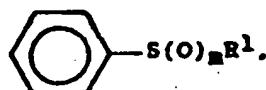
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R1 is $\text{CH}_3\text{CH}_2(\text{CH}_3)\text{CH}_2$, alkyl of 5-12 carbon atoms, cyclohexyl,



when R is

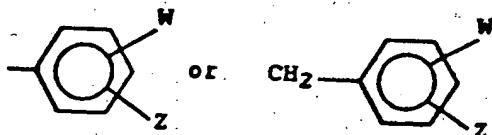
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15

R¹
R²can be in addition alkyl of 3-4 carbon atoms;
is

20



25

R³
R⁴
R⁵, R⁶, R⁷ and R⁸is H, alkoxy of 1-3 carbon atoms, or alkyl of 1-2 carbon atoms;
is CO₂H or CO₂R¹¹;
are independently H, F, Cl, Br, I, CH₃, CF₃, SCH₃ or CH₂CH₃, at least two of
R⁵, R⁶, R⁷ and R⁸ being H;R⁹ and R^{8A}
R¹¹are independently H or alkyl of 1 to 3 carbon atoms;
is (CH₂)₂₋₄NR⁹R^{8A};

W, Y and Z

are independently H, F, Cl, Br, alkyl of 1-5 carbon atoms, NO₂, OH, CF₃ or
OCH₃;m
is 0 or 1; or

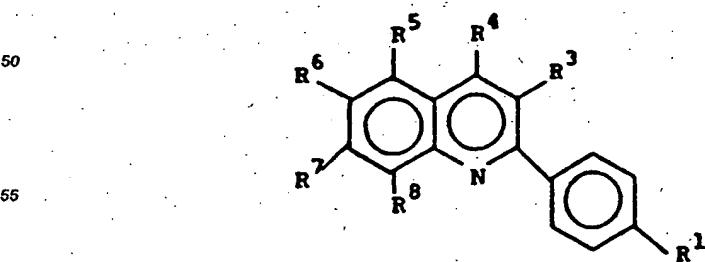
a pharmaceutically suitable salt thereof;

with the following provisos:

(1) R⁵, R⁶ and R⁷ cannot all be H;(2) when R⁴ is CO₂CH₂CH₂N(CH₃)₂, R⁶ is CH₂CH₃, or R⁷ is Cl, R¹ cannot be cyclohexyl;(3) when R¹ is cyclohexyl and R³ is H, R⁶ must be Cl or F, but R⁶ and R⁸ cannot both be Cl; and(4) when R⁶ is CH₃, then R⁷ cannot be Cl.

for the preparation of a medicament for the treatment of a skin or muco-epithelial disease in a mammal.

45 2. The use of Claim 1 wherein the compound has the formula:



wherein

5 R¹ is cyclohexyl; phenyl; phenyl substituted with one halogen, alkyl of 1-5 carbon atoms or CF₃; phenoxy; or phenoxy substituted with one halogen or alkyl of 1-5 carbon atoms;

10 R³ is H or alkyl of 1-2 carbon atoms;

15 R⁴ is CO₂H, a sodium or potassium salt thereof; or CO₂R¹¹;

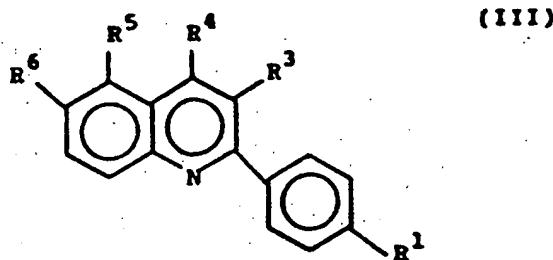
20 R⁵ and R⁶ are independently H, halogen, CH₃ or CF₃;

25 R⁷ and R⁸ are independently H or halogen;

30 R¹¹ is (CH₂)₂₋₄NR⁹R^{9A}; and

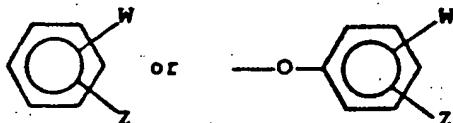
35 R⁹ and R^{9A} are independently alkyl of 1 to 3 carbon atoms, or a pharmaceutically suitable salt thereof; provided that R⁵, R⁶ and R⁷ cannot all be H and that when R¹ is cyclohexyl and R³ is H, R⁶ must be Cl or F, but R⁶ and R⁸ cannot both be Cl, and when R⁶ is CH₃, then R⁷ cannot be Cl.

15 3. The use of Claim 1 wherein the compound has the formula:



wherein

30 R¹ is cyclohexyl,



40 R³ is H or alkyl of 1-2 carbon atoms;

45 R⁴ is CO₂H, a sodium or potassium salt thereof, or CO₂R¹¹;

50 R⁵ and R⁶ are independently H, halogen or CF₃ provided that both R⁵ and R⁶ are not hydrogen;

55 R¹¹ is (CH₂)₂₋₄NR⁹R^{9A}; and

60 R⁹ and R^{9A} are independently alkyl of 1 to 3 carbon atoms, and W and Z are independently H, halogen, alkyl of 1-5 carbon atoms or CF₃; provided that when R¹ is phenyl or phenoxy, and R⁵ is H, then R⁶ cannot be Br; and that when R¹ is cyclohexyl and R³ is H, R⁶ must be Cl or F.

4. The use of Claim 1 wherein the compound is 2-(1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

5. The use of Claim 1 wherein the compound is 6-fluoro-3-methyl-2-(4-phenoxyphenyl)-4-quinolinecarboxylic acid, sodium or potassium salt.

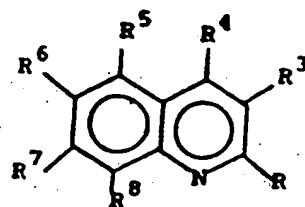
6. The use of Claim 1 wherein the compound is 2-(4'-bromo-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

7. The use of Claim 1 wherein the compound is 2-(2'-fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

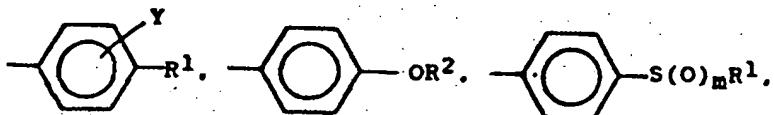
8. The use of Claim 1 wherein the compound is 2-(1,1'-biphenyl-4-yl)-5-chloro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

9. The use of Claim 1 wherein the compound is administered in combination with a steroid drug.

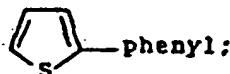
10. A pharmaceutical composition, adapted for topical administration, to the exclusion of internal administration, comprising a carrier suitable for topical formulation and an efficacious amount of a compound having the formula:



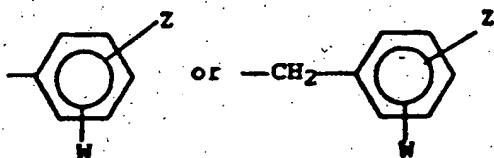
20 wherein
R is



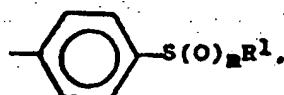
30 or



R1 is cyclohexyl,

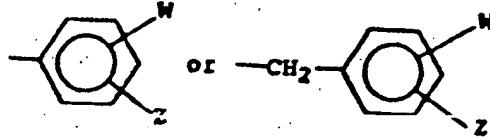


when R is



55 R1
R2 can be in addition alkyl of 3-4 carbon atoms;
is

5



10 R^3 is H, alkoxy of 1-3 carbon atoms, or alkyl of 1-2 carbon atoms;
 R^4 is CO_2H or CO_2R^{11} ;
 15 R^5 , R^6 , R^7 and R^8 are independently H, F, Cl, Br, I, CH_3 , CF_3 , SCH_3 or CH_2CH_3 , at least two of R^5 , R^6 , R^7 and R^8 being H;
 R^9 and R^{9A} are independently H or alkyl of 1 to 3 carbon atoms;
 20 R^{11} is $(CH_2)_{2-4}NR^9R^{9A}$;
 25 W , Y , and Z are independently H, F, Cl, Br, alkyl of 1-5 carbon atoms, NO_2 , OH , CF_3 or OCH_3 ;
 m is 0 or 1; or
 a pharmaceutically suitable salt thereof;
 with the following provisos:
 (1) when R^4 is CO_2H , R^1 is phenyl or R^2 is phenyl and R^5 , R^7 and R^8 are H, R^6 cannot be Br;
 (2) R^5 , R^6 and R^7 cannot all be H;
 (3) when R^4 is $CO_2CH_2CH_2N(CH_3)_2$, R^5 is CH_2CH_3 , or R^7 is Cl, R^1 cannot be cyclohexyl; and
 (4) when R^1 is cyclohexyl and R^3 is H, R^6 must be Cl or F, but R^6 and R^8 cannot both be Cl; and
 (5) when R^6 is CH_3 , R^7 cannot be Cl.

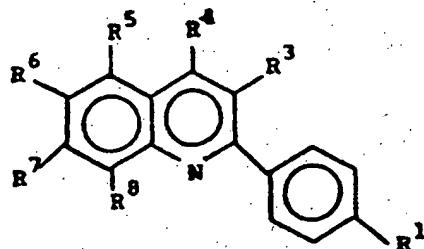
25

11. The topical composition of Claim 10 wherein the compound has the formula:

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(III)

35



40

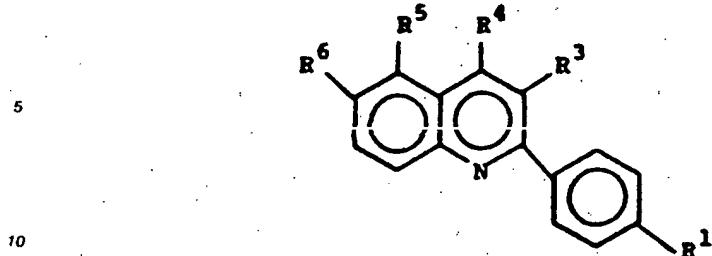
wherein

R^1 is cyclohexyl; phenyl; phenyl substitute with one halogen, alkyl of 1-5 carbon atoms or CF_3 ; phenoxy; or phenoxy substituted with one halogen or alkyl of 1-5 carbon atoms;
 45 R^3 is H or alkyl of 1-2 carbon atoms;
 R^4 is CO_2H , a sodium or potassium salt thereof; or CO_2R^{11} ;
 R^5 and R^6 are independently H, halogen, CH_3 or CF_3 ;
 R^7 and R^8 are independently H or halogen;
 R^{11} is $(CH_2)_{2-4}NR^9R^{9A}$; and
 50 R^9 and R^{9A} are independently alkyl of 1 to 3 carbon atoms,
 or a pharmaceutically suitable salt thereof;
 provided that R^5 , R^6 and R^7 cannot all be H and that when R^1 is cyclohexyl and R^3 is H, R^6 must be Cl or F, but R^6 and R^8 cannot both be Cl, and when R^6 is CH_3 , then R^7 cannot be Cl.

55

12. The topical composition of Claim 10 wherein the compound has the formula:

(III)



wherein
15 R¹ is cyclohexyl,

20

25 R³ is H or alkyl of 1-2 carbon atoms;
R⁴ is CO₂H, a sodium or potassium salt thereof, or CO₂R¹¹;
R⁵ and R⁶ are independently H, halogen or CF₃ provided that both R⁵ and R⁶ are not hydrogen;
R¹¹ is (CH₂)₂₋₄NR⁹R^{9A}; and
R⁹ and R^{9A} are independently alkyl of 1 to 3 carbon atoms, and
W and Z are independently H, halogen, alkyl of 1-5 carbon atoms or CF₃;
30 provided that when R¹ is phenyl or phenoxy, and R⁵ is H, then R⁶ cannot be Br; and that when R¹ is cyclohexyl and R³ is H, R⁶ must be Cl or F.

35 13. The topical composition of Claim 10 wherein the compound is 2-(1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinoline-carboxylic acid, sodium or potassium salt.

14. The topical composition of Claim 10 wherein the compound is 6-fluoro-3-methyl-2-(4-phenoxyphenyl)-4-quinoline-carboxylic acid, sodium or potassium salt.

15. The topical composition of Claim 10 wherein the compound is 2-(4'-bromo-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinoline-carboxylic acid, sodium or potassium salt.

40 16. The topical composition of Claim 10 wherein the compound is 2-(2'-fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinoline-carboxylic acid, sodium or potassium salt.

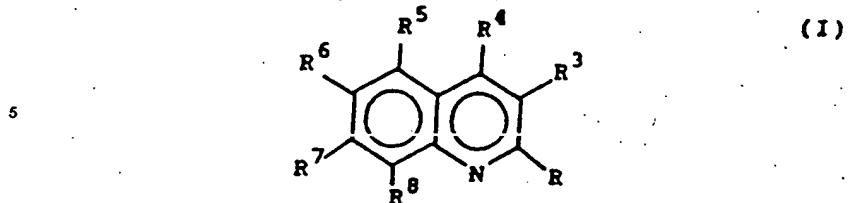
17. The topical composition of Claim 10 wherein the compound is 2-(1,1'-biphenyl-4-yl)-5-chloro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

45 18. The topical composition of Claim 10 wherein the compound is present in combination with a steroid drug.

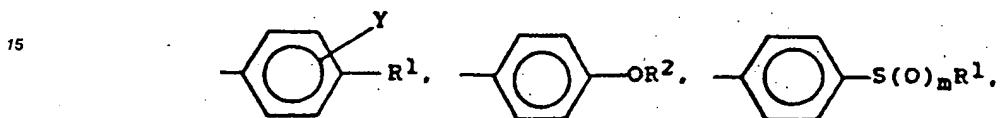
50 **Claims for the following Contracting States : ES, GR**

1. Method of preparing pharmaceutical compositions adapted for topical administration, to the exclusion of internal administration, comprising containing compounds having the formula:

55



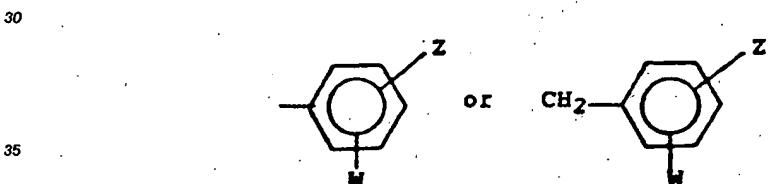
10 wherein R is



20 or



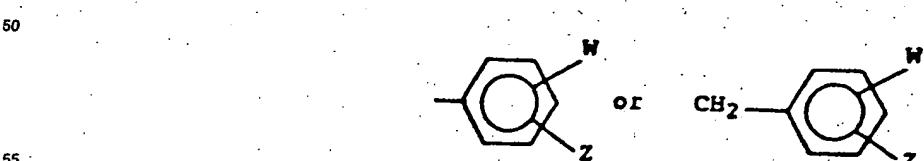
R1 is $\text{CH}_3\text{CH}_2(\text{CH}_3)\text{CH}_2$, alkyl of 5-12 carbon atoms, cyclohexyl,



35 when R is



45 R¹ can be in addition alkyl of 3-4 carbon atoms;
R² is



55 R³ is H, alkoxy of 1-3 carbon atoms, or alkyl of 1-2 carbon atoms;

R⁴ is CO₂H or CO₂R¹¹;
 R⁵, R⁶, R⁷ and R⁸ are independently H, F, Cl, Br, I, CH₃, CF₃, SCH₃ or CH₂CH₃, at least two of R⁵, R⁶, R⁷ and R⁸ being H;
 R⁹ and R^{9A} are independently H or alkyl of 1 to 3 carbon atoms;
 R¹¹ is (CH₂)₂₋₄NR⁹R^{9A};
 W, Y and Z are independently H, F, Cl, Br, alkyl of 1-5 carbon atoms, NO₂, OH, CF₃ or OCH₃;
 m is 0 or 1; or

a pharmaceutically suitable salt thereof;

with the following provisos:

- (1) R⁵, R⁶ and R⁷ cannot all be H;
- (2) when R⁴ is CO₂CH₂CH₂N(CH₃)₂, R⁶ is CH₂CH₃, or R⁷ is Cl, R¹ cannot be cyclohexyl;
- (3) when R¹ is cyclohexyl and R³ is H, R⁶ must be Cl or F, but R⁵ and R⁸ cannot both be Cl; and
- (4) when R⁶ is CH₃, then R⁷ cannot be Cl,

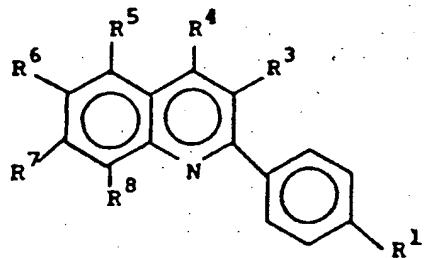
comprising compounding compounds of formula I with suitable pharmaceutical carriers and adjuvants for preparing medicaments for the treatment of a skin or muco-epithelial disease in a mammal.

2. The method of Claim 1 wherein the compound has the formula:

20

(II)

25



30

wherein

R¹

is cyclohexyl; phenyl; phenyl substituted with one halogen, alkyl of 1-5 carbon atoms or CF₃; phenoxy; or phenoxy substituted with one halogen or alkyl of 1-5 carbon atoms;

R³

is H or alkyl of 1-2 carbon atoms;

R⁴

is CO₂H, a sodium or potassium salt thereof; or CO₂R¹¹;

R⁵ and R⁶

are independently H, halogen CH₃ or CF₃;

R⁷ and R⁸

are independently H or halogen;

R¹¹

is (CH₂)₂₋₄NR⁹R^{9A}; and

R⁹ and R^{9A}

are independently alkyl of 1 to 3 carbon atoms,

or a pharmaceutically suitable salt thereof;

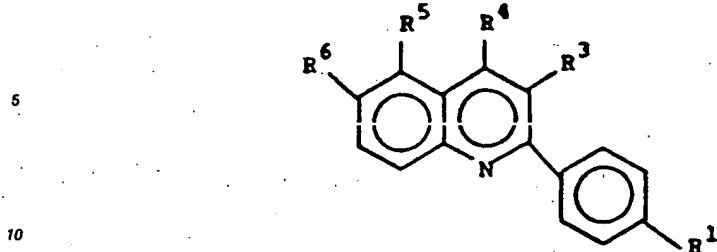
provided that R⁵, R⁶ and R⁷ cannot all be H and that when R¹ is cyclohexyl and R³ is H, R⁶ must be Cl or F, but R⁵ and R⁸ cannot both be Cl, and when R⁶ is CH₃, then R⁷ cannot be Cl.

3. The method of Claim 1 wherein the compound has the formula:

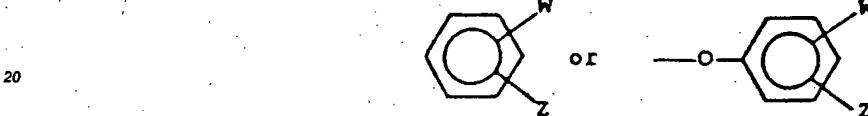
50

55

(III)



wherein
15 R¹ is cyclohexyl



25 R³ is H or alkyl of 1-2 carbon atoms;
R⁴ is CO₂H, a sodium or potassium salt thereof, or CO₂R¹¹;
R⁵ and R⁶ are independently H, halogen or CF₃ provided that both R⁵ and R⁶ are not hydrogen;
R¹¹ is (CH₂)₂-NR⁹R^{9A}; and
R⁹ and R^{9A} are independently alkyl of 1 to 3 carbon atoms, and
W and Z are independently H, halogen, alkyl of 1-5 carbon atoms or CF₃;
30 provided that when R¹ is phenyl or phenoxy and R⁵ is H, then R⁶ cannot be Br; and that when R¹ is cyclohexyl and R³ is H, R⁶ must be Cl or F.

4. The method of Claim 1 wherein the compound is 2-(1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

35 5. The method of Claim 1 wherein the compound is 6-fluoro-3-methyl-2-(4-phenoxyphenyl)-4-quinolinecarboxylic acid, sodium or potassium salt.

6. The method of Claim 1 wherein the compound is 2-(4'-bromo-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

40 7. The method of Claim 1 wherein the compound is 2-(2'-fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

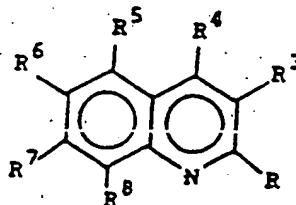
45 8. The method of Claim 1 wherein the compound is 2-(1,1'-biphenyl-4-yl)-5-chloro-3-methyl-4-quinolinecarboxylic acid, sodium or potassium salt.

9. The method of Claim 1 wherein the compound is administered in combination with a steroid drug.

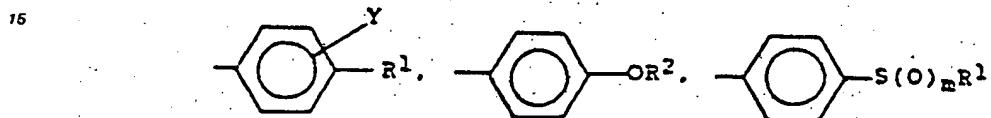
50 Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verwendung von Verbindungen, welche die Formel



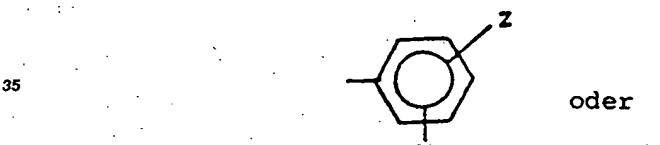
10 besitzen, worin
R



20 oder



ist;
30 R¹ CH₃CH₂(CH₃)CH, Alkyl mit 5-12 Kohlenstoff-Atomen, Cyclohexyl,

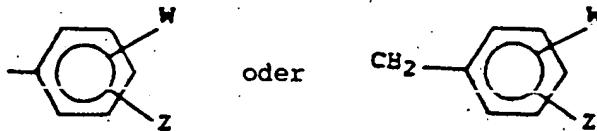


40 ist;
wenn R



50 ist, kann
R¹
R² zusätzlich Alkyl mit 3-4 Kohlenstoff-Atomen sein;

55



10 R³ ist; H, Alkoxy mit 1-3 Kohlenstoff-Atomen oder Alkyl mit 1-2 Kohlenstoff-Atomen ist;

11 R⁴ CO₂H oder CO₂R¹¹ ist;

12 R⁵, R⁶, R⁷ und R⁸ unabhängig H, F, Cl, Br, I, CH₃, CF₃, SCH₃ oder CH₂CH₃ sind, wobei wenigstens zwei von R⁵, R⁶, R⁷ und R⁸ H sind;

13 R⁹ und R^{9A} unabhängig H oder Alkyl mit 1 bis 3 Kohlenstoff-Atomen sind;

14 R¹¹ (CH₂)₂-NR⁹R^{9A} ist;

15 W, Y und Z unabhängig H, F, Cl, Br, Alkyl mit 1-5 Kohlenstoff-Atomen, NO₂, OH, CF₃ oder OCH₃ sind;

16 m 0 oder 1 ist; oder

17 20 ein pharmazeutisch geeignetes Salz derselben; mit den folgenden Maßgaben:

18 (1) R⁵, R⁶ und R⁷ können nicht alle H sein;

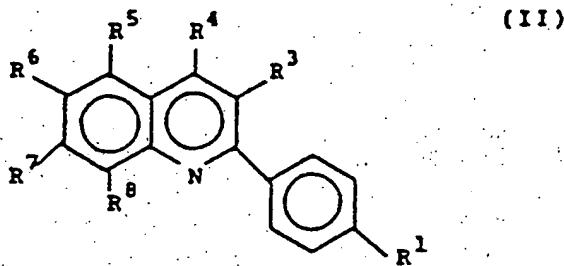
19 (2) wenn R⁴ CO₂CH₂CH₂N(CH₃)₂ ist, ist R⁶ CH₂CH₃, oder wenn R⁷ Cl ist, kann R¹ nicht Cyclohexyl sein;

20 (3) wenn R¹ Cyclohexyl ist und R³ H ist, muß R⁶ Cl oder F sein, aber R⁶ und R⁸ können nicht beide Cl sein; und

21 (4) wenn R⁶ CH₃ ist, dann kann R⁷ nicht Cl sein,

22 zur Herstellung eines Medikaments zur Behandlung einer Haut- oder Schleimhautepithel-Krankheit in einem Säuger.

23 30 2. Verwendung nach Anspruch 1, wobei die Verbindung die Formel



24 45 besitzt, worin

25 R¹ Cyclohexyl; Phenyl; mit einem Halogen, Alkyl mit 1-5 Kohlenstoff-Atomen oder CF₃ substituiertes Phenyl; Phenoxy oder mit einem Halogen oder Alkyl mit 1-5 Kohlenstoff-Atomen substituiertes Phenoxy ist;

26 R³ H oder Alkyl mit 1-2 Kohlenstoff-Atomen ist;

27 R⁴ CO₂H, dessen Natrium- oder Kaliumsalz, oder CO₂R¹¹ ist;

28 R⁵ und R⁶ unabhängig H, Halogen, CH₃ oder CF₃ sind;

29 R⁷ und R⁸ unabhängig H oder Halogen sind;

30 R¹¹ (CH₂)₂-NR⁹R^{9A} ist; und

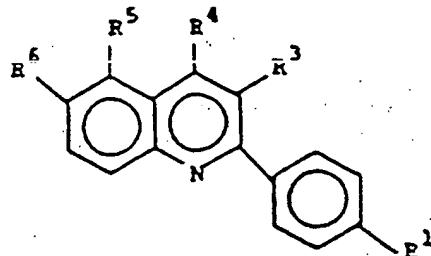
31 R⁹ und R^{9A} unabhängig Alkyl mit 1 bis 3 Kohlenstoff-Atomen sind,

32 55 oder ein pharmazeutisch geeignetes Salz derselben;

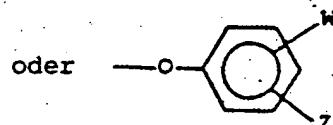
33 vorausgesetzt, daß R⁵, R⁶ und R⁷ nicht alle H sein können, und daß, wenn R¹ Cyclohexyl ist und R³ H ist, R⁶ Cl oder F sein muß; aber R⁶ und R⁸ nicht beide Cl sein können, und wenn R⁶ CH₃ ist, R⁷ dann nicht Cl sein kann.

3. Verwendung nach Anspruch 1, wobei die Verbindung die Formel

(III)



15 besitzt, worin
R¹ Cyclohexyl,



25 ist;

R³ H oder Alkyl mit 1-2 Kohlenstoff-Atomen ist;

R⁴ CO₂H, dessen Natrium- oder Kaliumsalz, oder CO₂R¹¹ ist;

R⁵ und R⁶ unabhängig H, Halogen, oder CF₃ sind, vorausgesetzt, daß R⁵ und R⁶ nicht beide Wasserstoff sind;

R¹¹ (CH₂)₂-NR⁹R^{9A} ist; und

R⁹ und R^{9A} unabhängig Alkyl mit 1 bis 3 Kohlenstoff-Atomen sind, und

W und Z unabhängig H, Halogen, Alkyl mit 1-5 Kohlenstoff-Atomen oder CF₃ sind;

vorausgesetzt daß, wenn R¹ Phenyl oder Phenoxy ist und R⁵ H ist, R⁶ dann nicht Br sein kann, und daß, wenn R¹ Cyclohexyl ist und R³ H ist, R⁶ Cl oder F sein muß.

4. Verwendung nach Anspruch 1, wobei die Verbindung 2-(1,1'-Biphenyl-4-yl)-6-fluor-3-methyl-4-chinolin-carbonsäure, -natrium- oder -kaliumsalz ist.

40 5. Verwendung nach Anspruch 1, wobei die Verbindung 6-Fluor-3-methyl-2-(4-phenoxyphenyl)-4-chinolin-carbonsäure, -natrium- oder -kaliumsalz ist.

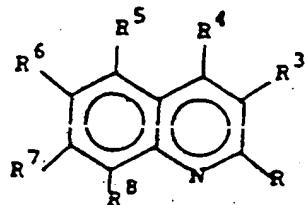
6. Verwendung nach Anspruch 1, wobei die Verbindung 2-(4'-Brom-1,1'-biphenyl-4-yl)-6-fluor-3-methyl-4-chinolin-carbonsäure, -natrium- oder -kaliumsalz ist.

45 7. Verwendung nach Anspruch 1, wobei die Verbindung 2-(2'-Fluor-1,1'-biphenyl-4-yl)-6-fluor-3-methyl-4-chinolin-carbonsäure, -natrium- oder -kaliumsalz ist.

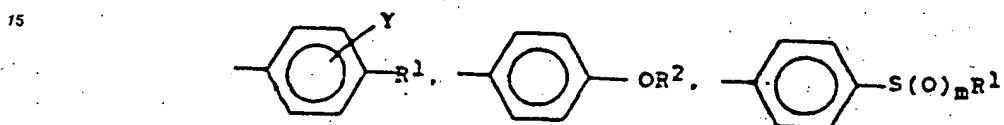
8. Verwendung nach Anspruch 1, wobei die Verbindung 2-(1,1'-Biphenyl-4-yl)-5-chlor-3-methyl-4-chinolin-carbonsäure, -natrium- oder -kaliumsalz ist.

50 9. Verwendung nach Anspruch 1, wobei die Verbindung in Kombination mit einem Steroidwirkstoff verabreicht wird.

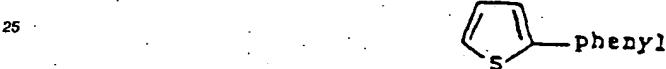
55 10. An die topische Verabreichung, unter Ausschluß der inneren Verabreichung, angepaßte pharmazeutische Zusammensetzung, umfassend einen zur topischen Formulierung geeigneten Träger und eine wirksame Menge einer Verbindung, welche die Formel



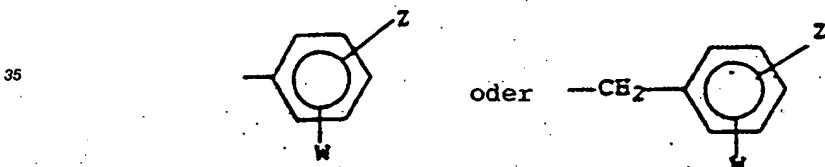
10 besitzt, worin
R



20 oder



30 ist;
R¹ Cyclohexyl,

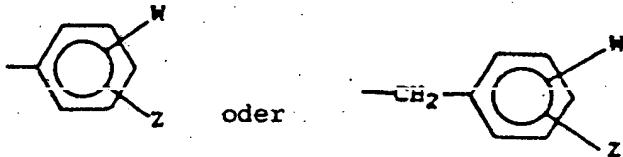


40 ist;
wenn R



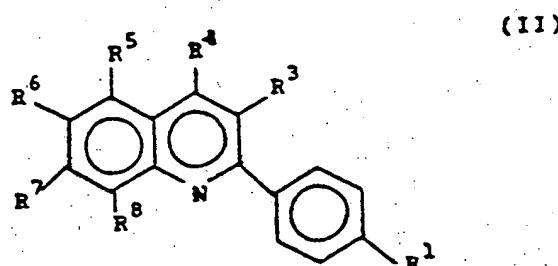
50 ist; kann
R¹
R² zusätzlich Alkyl mit 3-4 Kohlenstoff-Atomen sein;

55



10		ist;
	R^3	H, Alkoxy mit 1-3 Kohlenstoff-Atomen oder Alkyl mit 1-2 Kohlenstoff-Atomen
		ist;
15	R^4	CO_2H oder CO_2R^{11} ist;
	R^5, R^6, R^7 und R^8	unabhängig H, F, Cl, Br, I, CH_3 , CF_3 , SCH_3 oder CH_2CH_3 sind, wobei wenigstens zwei von R^5 , R^6 , R^7 und R^8 H sind;
	R^9 und R^{9A}	unabhängig H oder Alkyl mit 1 bis 3 Kohlenstoff-Atomen sind;
	R^{11}	$(CH_2)_{2-4}NR^9R^{9A}$ ist;
20	W, Y und Z	unabhängig H, F, Cl, Br, Alkyl mit 1-5 Kohlenstoff-Atomen, NO_2 , OH, CF_3 oder OCH_3 sind;
	m	0 oder 1 ist; oder
		ein pharmazeutisch geeignetes Salz derselben;
		mit den folgenden Maßgaben:
25		(1) wenn R^4 CO_2H ist, ist R^1 Phenyl oder wenn R^2 Phenyl ist und R^5, R^7 und R^8 H sind, kann R^6 nicht Br sein;
		(2) R^5, R^6 und R^7 können nicht alle H sein;
		(3) wenn R^4 $CO_2CH_2CH_2N(CH_3)_2$ ist, ist R^6 CH_2CH_3 , oder wenn R^7 Cl ist, kann R^1 nicht Cyclohexyl sein;
30		(4) wenn R^1 Cyclohexyl ist und R^3 H ist, muß R^6 Cl oder F sein, aber R^6 und R^8 können nicht beide Cl sein; und
		(5) wenn R^6 CH_3 ist, kann R^7 nicht Cl sein.

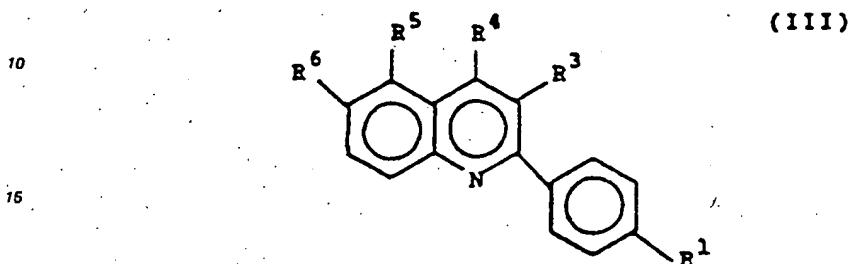
11. Topische Zusammensetzung nach Anspruch 10, wobei die Verbindung die Formel



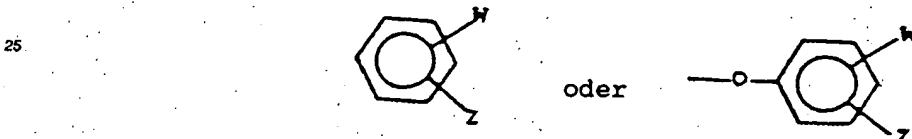
	besitzt, worin
50	<p>R¹ Cyclohexyl; Phenyl; mit einem Halogen, Alkyl mit 1-5 Kohlenstoff-Atomen oder CF₃ substituiertes Phenyl; Phenoxy oder mit einem Halogen oder Alkyl mit 1-5 Kohlenstoff-Atomen substituiertes Phenoxy ist;</p>
	<p>R³ H oder Alkyl mit 1-2 Kohlenstoff-Atomen ist;</p>
	<p>R⁴ CO₂H, dessen Natrium- oder Kaliumsalz, oder CO₂R¹¹ ist;</p>
55	<p>R⁵ und R⁶ unabhängig H, Halogen, CH₃ oder CF₃ sind;</p>
	<p>R⁷ und R⁸ unabhängig H oder Halogen sind;</p>
	<p>R¹¹ (CH₂)₂₋₄NR⁹R^{9A} ist; und</p>
	<p>R⁹ und R^{9A} unabhängig Alkyl mit 1 bis 3 Kohlenstoff-Atomen sind, oder ein pharmazeutisch geeignetes Salz derselben;</p>

vorausgesetzt, daß R⁵, R⁶ und R⁷ nicht alle H sein können, und daß, wenn R¹ Cyclohexyl ist und R³ H ist, R⁶ Cl oder F sein muß, aber R⁶ und R⁸ nicht beide Cl sein können, und wenn R⁶ CH₃ ist, R⁷ dann nicht Cl sein kann.

5 12. Topische Zusammensetzung nach Anspruch 10, worin die Verbindung die Formel



20 besitzt, worin
R¹ Cyclohexyl,



35 ist:
R³ H oder Alkyl mit 1-2 Kohlenstoff-Atomen ist;
R⁴ CO₂H, dessen Natrium- oder Kaliumsalz, oder CO₂R¹¹ ist;
R⁵ und R⁶ unabhängig H, Halogen, oder CF₃ sind, vorausgesetzt, daß R⁵ und R⁶ nicht beide Wasserstoff sind;
R¹¹ (CH₂)₂-NR⁹R^{8A} ist; und
R⁹ und R^{8A} unabhängig Alkyl mit 1 bis 3 Kohlenstoff-Atomen sind, und
W und Z unabhängig H, Halogen, Alkyl mit 1-5 Kohlenstoff-Atomen oder CF₃ sind;
vorausgesetzt daß, wenn R¹ Phenyl oder Phenoxy ist und R⁵ H ist, R⁶ dann nicht Br sein kann, und
daß, wenn R¹ Cyclohexyl ist und R³ H ist, R⁶ Cl oder F sein muß.

40 13. Topische Zusammensetzung nach Anspruch 10, worin die Verbindung 2-(1,1'-Biphenyl-4-yl)-6-fluor-3-methyl-4-chinolincarbonsäure, -natrium- oder -kaliumsalz ist.

45 14. Topische Zusammensetzung nach Anspruch 10, worin die Verbindung 6-Fluor-3-methyl-2-(4-phenoxyphenyl)-4-chinolincarbonsäure, -natrium- oder -kaliumsalz ist.

50 15. Topische Zusammensetzung nach Anspruch 10, worin die Verbindung 2-(4'-Brom-1,1'-biphenyl-4-yl)-6-fluor-3-methyl-4-chinolincarbonsäure, -natrium- oder -kaliumsalz ist.

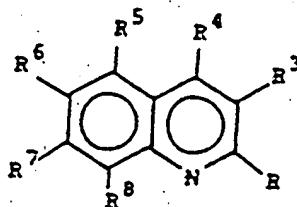
55 16. Topische Zusammensetzung nach Anspruch 10, worin die Verbindung 2-(2'-Fluor-1,1'-biphenyl-4-yl)-6-fluor-3-methyl-4-chinolincarbonsäure, -natrium- oder -kaliumsalz ist.

17. Topische Zusammensetzung nach Anspruch 10, worin die Verbindung 2-(1,1'-Biphenyl-4-yl)-5-chlor-3-methyl-4-chinolincarbonsäure, -natrium- oder -kaliumsalz ist.

55 18. Topische Zusammensetzung nach Anspruch 10, worin die Verbindung in Kombination mit einem Steroidwirkstoff vorliegt.

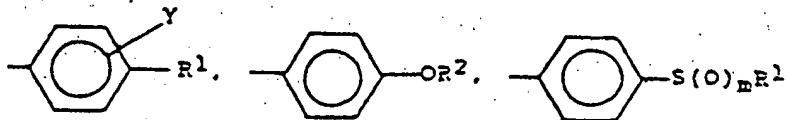
Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung an die topische Verabreichung, unter Ausschluß der inneren Verabreichung, angepaßter pharmazeutischer Zusammensetzungen, enthaltend Verbindungen, welche die Formel



(I)

besitzen, worin
R

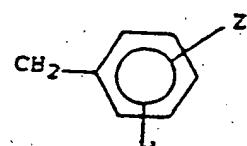
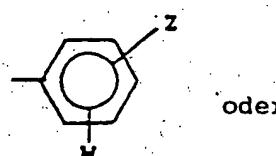


oder

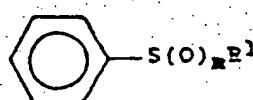


ist;

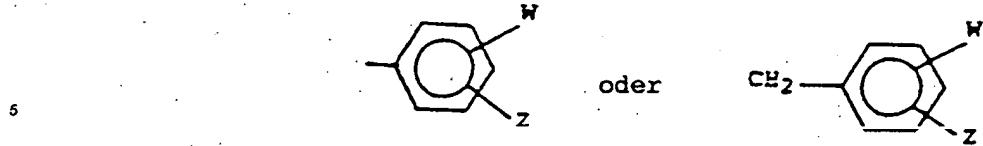
35 R1 CH₃CH₂(CH₃)CH₂, Alkyl mit 5-12 Kohlenstoff-Atomen, Cyclohexyl,



45 ist;
wenn R



55 Ist, kann
R¹
R² zusätzlich Alkyl mit 3-4 Kohlenstoff-Atomen sein;



ist;

10 R^3 H , Alkoxy mit 1-3 Kohlenstoff-Atomen oder Alkyl mit 1-2 Kohlenstoff-Atomen ist;

10 R^4 CO_2H oder CO_2R^{11} ist;

10 R^5 , R^6 , R^7 und R^8 unabhängig H , F , Cl , Br , I , CH_3 , CF_3 , SCH_3 oder CH_2CH_3 sind, wobei wenigstens zwei von R^5 , R^6 , R^7 und R^8 H sind;

15 R^9 und R^{9A} unabhängig H oder Alkyl mit 1 bis 3 Kohlenstoff-Atomen sind;

15 R^{11} $(CH_2)_2-4NR^9R^{9A}$ ist;

15 W , Y und Z unabhängig H , F , Cl , Br , Alkyl mit 1-5 Kohlenstoff-Atomen, NO_2 , OH , CF_3 oder OCH_3 sind;

20 m 0 oder 1 ist; oder

20 ein pharmazeutisch geeignetes Salz derselben; mit den folgenden Maßgaben:

20 (1) R^5 , R^6 und R^7 können nicht alle H sein;

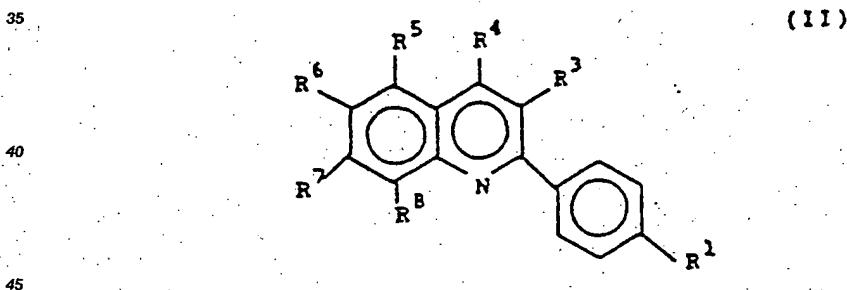
20 (2) wenn R^4 $CO_2CH_2CH_2N(CH_3)_2$ ist, ist R^6 CH_2CH_3 , oder wenn R^7 Cl ist, kann R^1 nicht Cyclohexyl sein;

25 (3) wenn R^1 Cyclohexyl ist und R^3 H ist, muß R^6 Cl oder F sein, aber R^6 und R^8 können nicht beide Cl sein; und

25 (4) wenn R^6 CH_3 ist, dann kann R^7 nicht Cl sein,

25 umfassend das Vermischen von Verbindungen der Formel (I) mit geeigneten pharmazeutischen Trägern und Adjuvantien zur Herstellung eines Medikaments zur Behandlung einer Haut- oder Schleimhautepithel-Krankheit in einem Säuger.

2. Verfahren nach Anspruch 1, wobei die Verbindung die Formel



besitzt, worin

45 R^1 Cyclohexyl; Phenyl; mit einem Halogen, Alkyl mit 1-5 Kohlenstoff-Atomen oder CF_3 substituiertes Phenyl; Phenoxy oder mit einem Halogen oder Alkyl mit 1-5 Kohlenstoff-Atomen substituiertes Phenoxy ist;

50 R^3 H oder Alkyl mit 1-2 Kohlenstoff-Atomen ist;

50 R^4 CO_2H , dessen Natrium- oder Kaliumsalz, oder CO_2R^{11} ist;

50 R^5 und R^6 unabhängig H , Halogen, CH_3 oder CF_3 sind;

50 R^7 und R^8 unabhängig H oder Halogenen sind;

55 R^{11} $(CH_2)_2-4NR^9R^{9A}$ ist; und

55 R^9 und R^{9A} unabhängig Alkyl mit 1 bis 3 Kohlenstoff-Atomen sind;

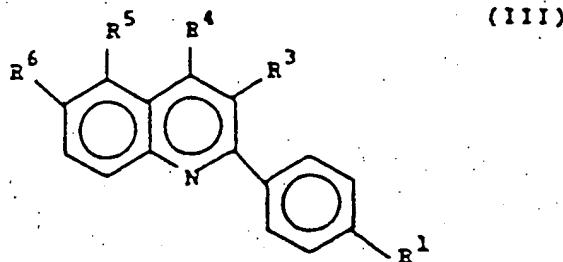
55 oder ein pharmazeutisch geeignetes Salz derselben;

55 vorausgesetzt, daß R^5 , R^6 und R^7 nicht alle H sein können, und daß, wenn R^1 Cyclohexyl ist und R^3 H

ist, R⁶ Cl oder F sein muß, aber R⁶ und R⁸ nicht beide Cl sein können, und wenn R⁶ CH₃ ist, R⁷ dann nicht Cl sein kann.

3. Verfahren nach Anspruch 1, worin die Verbindung die Formel

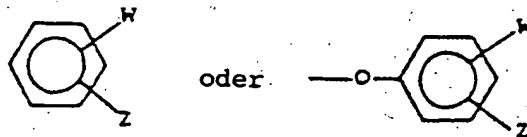
5



besitzt, worin

20 R¹ Cyclohexyl,

25



ist;

30 R³ H oder Alkyl mit 1-2 Kohlenstoff-Atomen ist;
 R⁴ CO₂H, dessen Natrium- oder Kaliumsalz, oder CO₂R¹¹ ist;
 R⁵ und R⁶ unabhängig H, Halogen, oder CF₃ sind, vorausgesetzt, daß R⁵ und R⁶ nicht beide Wasserstoff sind;
 R¹¹ (CH₂)₂-4NR⁹R^{9A} ist; und
 35 R⁸ und R^{9A} unabhängig Alkyl mit 1 bis 3 Kohlenstoff-Atomen sind, und
 W und Z unabhängig H, Halogen, Alkyl mit 1-5 Kohlenstoff-Atomen oder CF₃ sind;
 vorausgesetzt daß, wenn R¹ Phenyl oder Phenoxy ist und R⁵ H ist, R⁶ dann nicht Br sein kann, und daß, wenn R¹ Cyclohexyl ist und R³ H ist, R⁶ Cl oder F sein muß.

40 4. Verfahren nach Anspruch 1, worin die Verbindung 2-(1,1'-Biphenyl-4-yl)-6-fluor-3-methyl-4-chinolincarbonsäure, -natrium- oder -kaliumsalz ist.

5. Verfahren nach Anspruch 1, worin die Verbindung 6-Fluor-3-methyl-2-(4-phenoxyphenyl)-4-chinolincarbonsäure, -natrium- oder -kaliumsalz ist.

45 6. Verfahren nach Anspruch 1, worin die Verbindung 2-(4'-Brom-1,1'-biphenyl-4-yl)-6-fluor-3-methyl-4-chinolincarbonsäure, -natrium- oder -kaliumsalz ist.

7. Verfahren nach Anspruch 1, worin die Verbindung 2-(2'-Fluor-1,1'-biphenyl-4-yl)-6-fluor-3-methyl-4-chinolincarbon säure, -natrium- oder -kaliumsalz ist.

50 8. Verfahren nach Anspruch 1, worin die Verbindung 2-(1,1'-Biphenyl-4-yl)-5-chlor-3-methyl-4-chinolincarbonsäure, -natrium- oder -kaliumsalz ist.

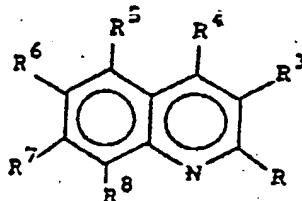
9. Verfahren nach Anspruch 1, worin die Verbindung in Kombination mit einem Steroidwirkstoff verabreicht wird.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Utilisation de composés ayant la formule:

5



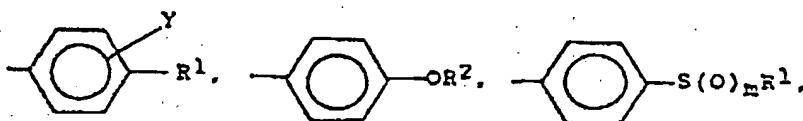
(I)

10

15 dans laquelle:

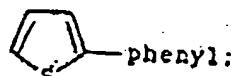
R est

20



ou

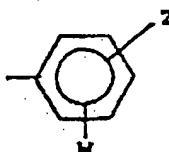
25



30

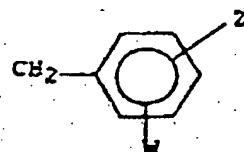
R1 est $\text{CH}_3\text{CH}_2(\text{CH}_3)\text{CH}$, un groupe alkyle comprenant 5 à 12 atomes de carbone, cyclohexyle;

35



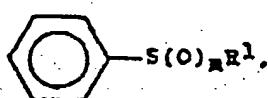
ou

40



quand R est

45



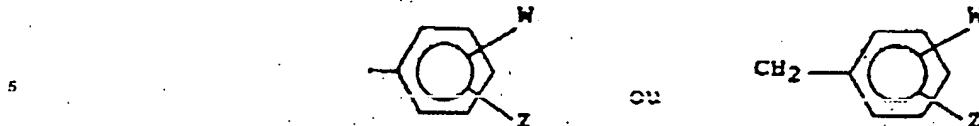
50

R1

R2

peut être en outre un groupe alkyle comprenant 3 ou 4 atomes de carbone;
est

55



10 **R³** est H, un groupe alkoxy comprenant 1 à 3 atomes de carbone, ou un groupe alkyle comprenant 1 ou 2 atomes de carbone;

10 **R⁴** est CO_2H ou CO_2R^{11} ;

10 **R⁵, R⁶, R⁷, et R⁸** sont indépendamment l'un de l'autre H, F, Cl, Br, I, CH_3 , CF_3 , SCH_3 ou CH_2CH_3 , au moins deux des groupes R^5 , R^6 , R^7 et R^8 étant H;

15 **R⁹ et R^{9A}** sont indépendamment l'un de l'autre H ou un groupe alkyle comprenant 1 à 3 atomes de carbone;

15 **R¹¹** est $(\text{CH}_2)_{2-4}\text{NR}^9\text{R}^{9A}$;

15 **W, Y et Z** sont indépendamment l'un de l'autre H, F, Cl, Br, un groupe alkyle comprenant 1 à 5 atomes de carbone, NO_2 , OH, CF_3 ou OCH_3 ;

20 **m** est 0 ou 1;

20 ou un de ses sels pharmaceutiquement acceptables;

aux conditions que:

(1) R^5 , R^6 et R^7 ne soient pas tous H;

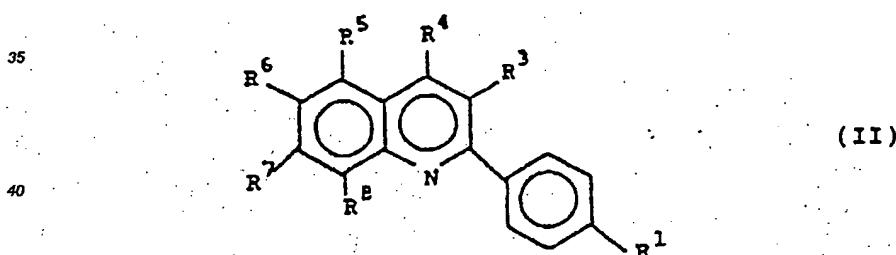
(2) lorsque R^4 est $\text{CO}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, R^6 est CH_2CH_3 ou R^7 est Cl, R^1 ne soit pas un groupe cyclohexyle;

25 (3) lorsque R^1 est un groupe cyclohexyle et R^3 est H, R^6 soit Cl ou F, R^6 et R^8 ne pouvant pas être tous deux Cl; et

(4) lorsque R^6 est CH_3 , alors R^7 ne soit pas Cl;

pour la préparation d'un médicament pour le traitement des maladies dermatologiques ou muco-épithéliales chez un mammifère.

30 2. L'utilisation selon la revendication 1 dans laquelle le composé présente la formule:



45 dans laquelle:

45 **R¹** est un groupe cyclohexyle, phényle, phényle substitué avec un halogène, un groupe alkyle comprenant 1 à 5 atomes de carbone ou CF_3 , un groupe phenoxy ou phénolxy substitué avec un halogène ou un groupe alkyle comprenant 1 à 5 atomes de carbone;

50 **R³** est H ou un groupe alkyle comprenant 1 ou 2 atomes de carbone;

50 **R⁴** est CO_2H , ou un sel de sodium ou de potassium en dérivant; ou CO_2R^{11} ;

50 **R⁵ et R⁶** sont indépendamment l'un de l'autre H, un halogène, CH_3 ou CF_3 ;

55 **R⁷ et R⁸** sont indépendamment l'un de l'autre H ou un halogène;

55 **R¹¹** est $(\text{CH}_2)_{2-4}\text{NR}^9\text{R}^{9A}$; et

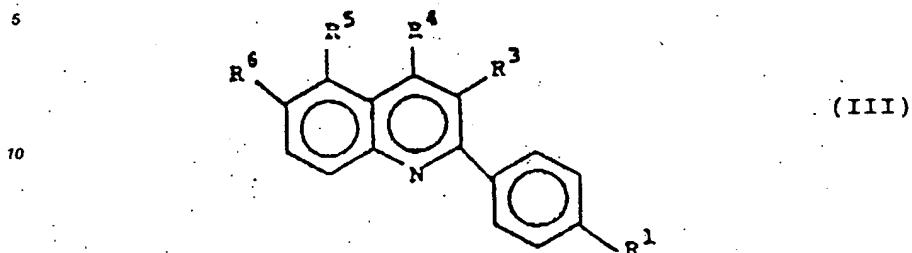
55 **R⁹ et R^{9A}** sont indépendamment l'un de l'autre un groupe alkyle comprenant 1 à 3 atomes de carbone,

ou un de ses sels pharmaceutiquement acceptables;

à la condition que R^5 , R^6 et R^7 ne soient pas tous H et que, lorsque R^1 est un groupe cyclohexyle et R^3 est H, R^6 soit Cl ou F, R^6 et R^8 ne pouvant pas être tous deux Cl, et que, lorsque R^6 est CH_3 , alors

R⁷ ne soit pas Cl.

3. L'utilisation selon la revendication 1, dans laquelle le composé présente la formule:



dans laquelle:

R¹ est un groupe cyclohexyle,



R³ est H ou un groupe alkyle comprenant 1 ou 2 atomes de carbone;

R⁴ est CO₂H, ou un sel de sodium ou de potassium en dérivant; ou CO²R¹¹;

R⁵ et R⁶ sont indépendamment l'un de l'autre H, halogène ou CF₃ pourvu que R⁵ et R⁶ ne soit pas tous deux de l'hydrogène;

30 R¹¹ est (CH₂)₂-NR⁸R^{9A}; et

R⁸ et R^{9A} sont indépendamment l'un de l'autre un groupe alkyle comprenant 1 à 3 atomes de carbone, et

W et Z sont indépendamment l'un de l'autre H, un halogène, un groupe alkyle comprenant 1 à 5 atomes de carbone ou CF₃;

35 à la condition que lorsque R¹ est un groupe phényle ou phenoxy, R⁵ soit H, R⁶ ne pouvant pas alors être Br; et que, lorsque R¹ est un groupe cyclohexyle et R³ est H, R⁶ soit Cl ou F.

4. L'utilisation selon la revendication 1, dans laquelle le composé est le sel de sodium ou de potassium de l'acide 2-(1,1'-biphenyl-4-yl)-6-fluoro-3-méthyl-4-quinoléinecarboxylique.

40 5. L'utilisation selon la revendication 1, dans laquelle le composé est le sel de sodium ou de potassium de l'acide 6-fluoro-3-méthyl-2-(4-phenoxyphényle)-4-quinoléinecarboxylique.

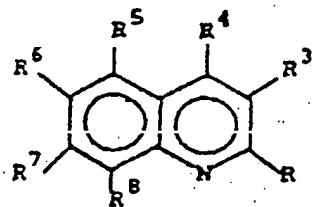
45 6. L'utilisation selon la revendication 1, dans laquelle le composé est le sel de sodium ou de potassium de l'acide 2-(4'-bromo-1,1'-biphenyl-4-yl)-6-fluoro-3-méthyl-4-quinoléinecarboxylique.

7. L'utilisation selon la revendication 1, dans laquelle le composé est le sel de sodium ou de potassium de l'acide 2-(2'-fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-méthyl-4-quinoléinecarboxylique.

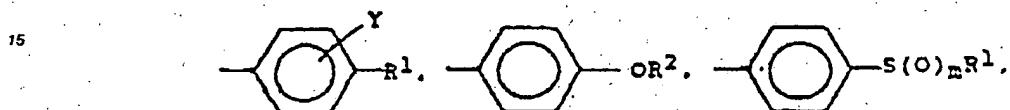
50 8. L'utilisation selon la revendication 1, dans laquelle le composé est le sel de sodium ou de potassium de l'acide 2-(1,1'-biphenyl-4-yl)-5-chloro-3-méthyl-4-quinoléinecarboxylique.

9. L'utilisation selon la revendication 1, dans laquelle le composé est administré en combinaison avec un médicament consistant en un stéroïde.

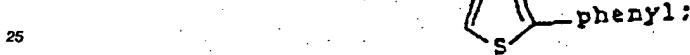
55 10. Une composition pharmaceutique convenant à une administration topique, à l'exclusion d'une administration interne, comprenant un support convenant à une formulation topique et une quantité efficace d'un composé ayant la formule:



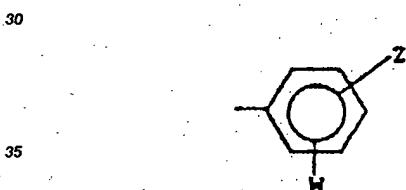
10
dans laquelle:
R est



20 ou



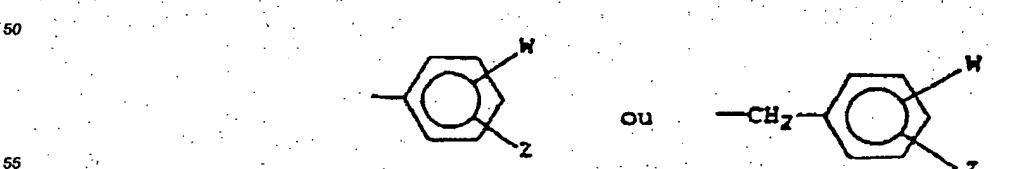
R¹ est un groupe cyclohexyle,



35 quand R est



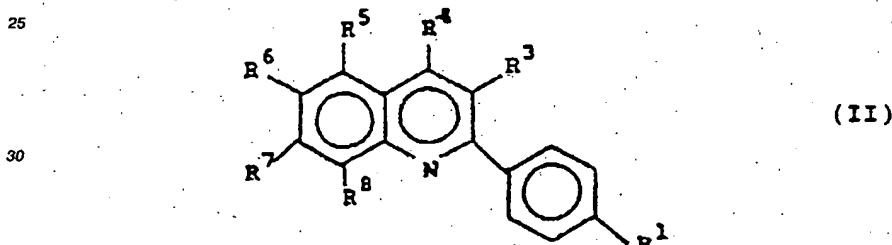
45 R¹
R² peut être en outre un groupe alkyle comprenant 3 ou 4 atomes de carbone;
est



55 R³ est H, un groupe alkoxy comprenant 1 à 3 atomes de carbone, ou un groupe

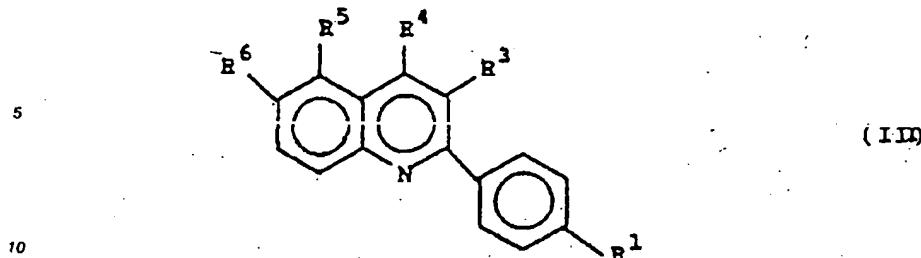
25 R^4 alkyle compréhendant 1 ou 2 atomes de carbone;
 est CO_2H ou CO_2R^{11} ;
 R^5 , R^6 , R^7 et R^8 sont indépendamment l'un de l'autre H, F, Cl, Br, I, CH_3 , CF_3 , SCH_3 ou
 CH_2CH_3 , au moins deux des groupes R^5 , R^6 , R^7 et R^8 étant H;
 5 R^9 et R^{9A} sont indépendamment l'un de l'autre H ou un groupe alkyle compréhendant 1 à 3
 atomes de carbone;
 R^{11} est $(CH_2)_2-NR^9R^{9A}$;
 W , Y et Z sont indépendamment l'un de l'autre H, F, Cl, Br, un groupe alkyle compréhendant
 1 à 5 atomes de carbone, NO_2 , OH, CF_3 ou OCH_3 ;
 10 m est 0 ou 1;
 ou un de ses sels pharmaceutiquement acceptables;
 aux conditions que:
 (1) lorsque R^4 est CO_2H , R^1 est un groupe phényle ou R^2 est un groupe phényle et R^5 , R^7 et R^8
 sont H, R^6 ne soit pas Br;
 15 (2) R^5 , R^6 et R^7 ne soient pas tous H;
 (3) lorsque R^4 est $CO_2CH_2CH_2N(CH_3)_2$, R^6 est CH_2CH_3 ou R^7 est Cl, R^1 ne soit pas un groupe
 cyclohexyle;
 (4) lorsque R^1 est un groupe cyclohexyle et R^3 est H, R^6 soit Cl ou F, R^6 et R^8 ne pouvant pas être
 tous deux Cl; et
 20 (5) lorsque R^6 est CH_3 , R^7 ne soit pas Cl.

11. La composition topique selon la revendication 10, dans laquelle le composé présente la formule:



35 dans laquelle:
 R^1 est un groupe cyclohexyle, phényle, phényle substitué avec un halogène, un groupe alkyle compréhendant 1 à 5 atomes de carbone ou CF_3 ; un groupe phén oxy ou phén oxy substitué avec un halogène ou un groupe alkyle compréhendant 1 à 5 atomes de carbone;
 40 R^3 est H ou un groupe alkyle compréhendant 1 ou 2 atomes de carbone;
 R^4 est CO_2H , ou le sel de sodium ou de potassium en dérivant; ou CO_2R^{11} ;
 R^5 et R^6 sont indépendamment l'un de l'autre H, un halogène, CH_3 ou CF_3 ;
 R^7 et R^8 sont indépendamment l'un de l'autre H ou un halogène;
 45 R^{11} est $(CH_2)_2-NR^9R^{9A}$; et
 R^9 et R^{9A} sont indépendamment l'un de l'autre un groupe alkyle compréhendant 1 à 3 atomes de carbone,
 ou un de ses sels pharmaceutiquement acceptables;
 à la condition que R^5 , R^6 et R^7 ne soient pas tous H et que, lorsque R^1 est un groupe cyclohexyle et
 R^3 est H, R^6 soit Cl ou F, R^6 et R^8 ne pouvant pas être tous deux Cl, et que, lorsque R^6 est CH_3 , alors
 50 R^7 ne soit pas Cl.

12. La composition topique selon la revendication 10, dans laquelle le composé présente la formule:

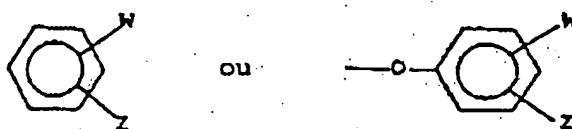


dans laquelle:

R¹ est un groupe cyclohexyle,

15

20



25 R³ est H ou un groupe alkyle comprenant 1 ou 2 atomes de carbone;
 R⁴ est CO₂H, ou le sel de sodium ou de potassium en dérivant; ou CO²R¹¹;
 R⁵ et R⁶ sont indépendamment l'un de l'autre H, un halogène ou CF₃ pourvu que R⁵ et R⁶ ne soient pas tous deux un hydrogène;

30 R¹¹ est (CH₂)₂-NR⁹R^{9A}; et
 R⁹ et R^{9A} sont indépendamment l'un de l'autre un groupe alkyle comprenant 1 à 3 atomes de carbone, et
 W et Z sont indépendamment l'un de l'autre H, un halogène, un groupe alkyle comprenant 1 à 5 atomes de carbone ou CF₃;

pourvu que, lorsque R¹ est un groupe phényle ou phenoxy et R⁵ est H, R⁶ ne soit pas Br; et que lorsque R¹ est un groupe cyclohexyle et R³ est H, R⁶ soit Cl ou F.

35 13. La composition topique selon la revendication 10, dans laquelle le composé est le sel de sodium ou de potassium de l'acide 2-(1,1'-biphényl-4-yl)-6-fluoro-3-méthyl-4-quinoléinecarboxylique.

14. La composition topique selon la revendication 10, dans laquelle le composé est le sel de sodium ou de potassium de l'acide 6-fluoro-3-méthyl-2-(4-phenoxyphényle)-4-quinoléinecarboxylique.

40 15. La composition topique selon la revendication 10, dans laquelle le composé est le sel de sodium ou de potassium de l'acide 2-(4'-bromo-1,1'-biphényl-4-yl)-6-fluoro-3-méthyl-4-quinoléinecarboxylique.

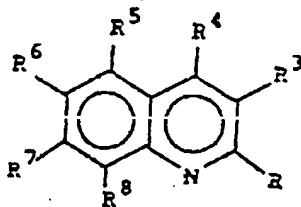
16. La composition topique selon la revendication 10, dans laquelle le composé est le sel de sodium ou de potassium de l'acide 2-(2'-fluoro-1,1'-biphényl-4-yl)-6-fluoro-3-méthyl-4-quinoléinecarboxylique.

45 17. La composition topique selon la revendication 10, dans laquelle le composé est le sel de sodium ou de potassium de l'acide 2-(1,1'-biphényl-4-yl)-5-chloro-3-méthyl-4-quinoléinecarboxylique.

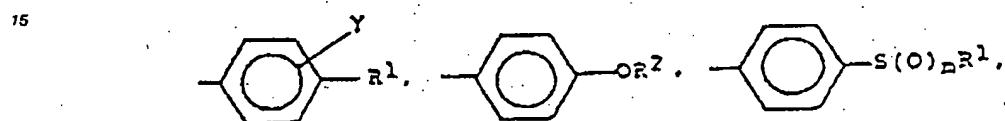
50 18. La composition topique selon la revendication 10, dans laquelle le composé est présent en combinaison avec un médicament consistant en un stéroïde.

Revendications pour les Etats contractants suivants : ES, GR

55 1. Procédé de préparation de compositions pharmaceutiques convenant à une administration topique, à l'exclusion d'une administration interne, comprenant des composés de formule:



10 dans laquelle:
R est



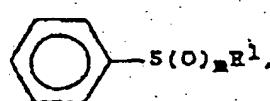
20 ou



30 R¹ est CH₃CH₂(CH₃)CH₂, un groupe alkyle comprenant 5 à 12 atomes de carbone, cyclohexyle;

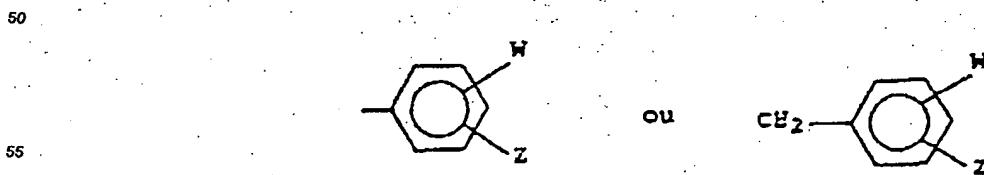


40 quand R est



R¹
R² peut être en outre un groupe alkyle comprenant 3 ou 4 atomes de carbone;

est



55 R³ est H, un groupe alkoxy comprenant 1 à 3 atomes de carbone, ou un groupe

R⁴ alkyle comprenant 1 ou 2 atomes de carbone;
 R⁵, R⁶, R⁷ et R⁸ est CO₂H ou CO₂R¹¹;

5 R⁹ et R^{9A} sont indépendamment l'un de l'autre H, F, Cl, Br, I, CH₃, CF₃, SCH₃ ou CH₂CH₃, au moins deux des groupes R⁵, R⁶, R⁷ et R⁸ étant H;

sont indépendamment l'un de l'autre H ou un groupe alkyle comprenant 1 à 3 atomes de carbone;

10 R¹¹ est (CH₂)₂-NR⁹R^{9A};

W, Y et Z sont indépendamment l'un de l'autre H, F, Cl, Br, un groupe alkyle comprenant 1 à 5 atomes de carbone, NO₂, OH, CF₃ ou OCH₃;

15 m est 0 ou 1;

ou un de ses sels pharmaceutiquement acceptables;

aux conditions que:

(1) R⁵, R⁶ et R⁷ ne soient pas tous H;

15 (2) lorsque R est CO₂CH₂CH₂N(CH₃)₂, R⁶ est CH₂CH₃ ou R est Cl, R¹ ne soit pas un groupe cyclohexyle;

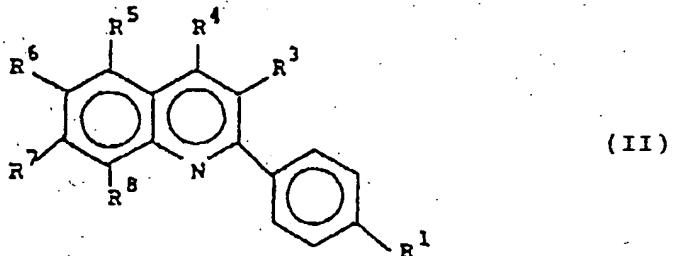
(3) lorsque R¹ est un groupe cyclohexyle et R³ est H, R⁶ soit Cl ou F, R⁵ et R⁸ ne pouvant pas être tous deux Cl; et

(4) lorsque R⁶ est CH₃, alors R⁷ ne soit pas Cl;

20 comprenant le mélange de composés de formule (I) avec des supports et des adjuvants pharmaceutiquement convenables pour la préparation de médicaments pour le traitement de maladies dermatologiques ou muco-épithéliales chez un mammifère.

2. Le procédé selon la revendication 1 dans lequel le composé présente la formule:

25



35

dans laquelle:

R¹ est un groupe cyclohexyle, phényle, phényle substitué avec un halogène, un groupe alkyle comprenant 1 à 5 atomes de carbone ou CF₃; un groupe phénoxy ou phenoxy substitué avec un halogène ou un groupe alkyle comprenant 1 à 5 atomes de carbone;

R³ est H ou un groupe alkyle comprenant 1 ou 2 atomes de carbone;

R⁴ est CO₂H, ou un sel de sodium ou de potassium en dérivant; ou CO₂R¹¹;

R⁵ et R⁶ sont indépendamment l'un de l'autre H, un halogène, CH₃ ou CF₃;

R⁷ et R⁸ sont indépendamment l'un de l'autre H ou un halogène;

R¹¹ est (CH₂)₂-NR⁹R^{9A}; et

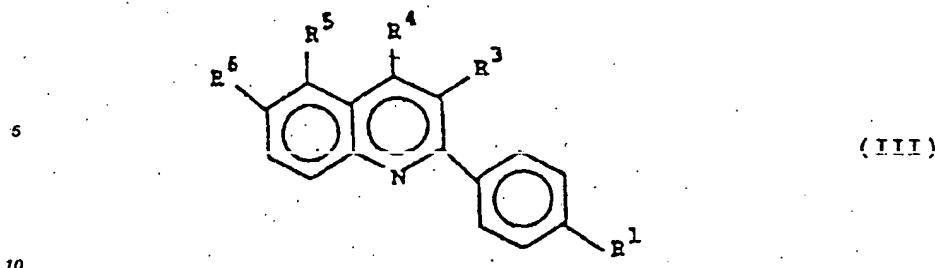
45 R et R^{9A} sont indépendamment l'un de l'autre un groupe alkyle comprenant 1 à 3 atomes de carbone,

ou un de ses sels pharmaceutiquement acceptables;

50 pourvu que, lorsque R⁵, R⁶ et R⁷ ne soient pas tous H et que lorsque R¹ est un groupe cyclohexyle et R³ est H, R⁶ soit Cl ou F, R⁶ et R⁸ ne pouvant pas être tous deux Cl, et que, lorsque R⁶ est CH₃, alors R⁷ ne soit pas Cl.

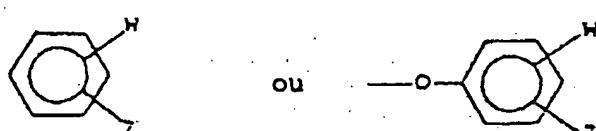
3. Le procédé selon la revendication 1, dans lequel le composé présente la formule:

55



dans laquelle:

15 R^1 est un groupe cyclohexyle,



25 R^3 est H ou un groupe alkyle comprenant 1 ou 2 atomes de carbone;

R^4 est CO_2H , ou un sel de sodium ou de potassium en dérivant; ou CO^2R^{11} ;

25 R^5 et R^6 sont indépendamment l'un de l'autre H, halogène ou CF_3 pourvu que R^5 et R^6 ne soit pas tous deux de l'hydrogène;

30 R^{11} est $(CH_2)_2-4NR^9R^{9A}$; et

R^9 et R^{9A} sont indépendamment l'un de l'autre un groupe alkyle comprenant 1 à 3 atomes de carbone, et

35 W et Z sont indépendamment l'un de l'autre H, un halogène, un groupe alkyle comprenant 1 à 5 atomes de carbone ou CF_3 ;

pourvu que, lorsque R^1 est un groupe phényle ou phenoxy, R^5 est H, R^6 ne soit pas Br; et que lorsque R^1 est un groupe cyclohexyle et R^3 est H, R^6 soit Cl ou F.

4. Le procédé selon la revendication 1, dans lequel le composé est le sel de sodium ou de potassium de l'acide 2-(1,1'-biphenyl-4-yl)-6-fluoro-3-méthyl-4-quinoléinecarboxylique.
5. Le procédé selon la revendication 1, dans lequel le composé est le sel de sodium ou de potassium de l'acide 6-fluoro-3-méthyl-2-(4-phenoxyphényle)-4-quinoléinecarboxylique.
- 40 6. Le procédé selon la revendication 1, dans lequel le composé est le sel de sodium ou de potassium de l'acide 2-(4'-bromo-1,1'-biphenyl-4-yl)-6-fluoro-3-méthyl-4-quinoléinecarboxylique.
7. Le procédé selon la revendication 1, dans lequel le composé est le sel de sodium ou de potassium de l'acide 2-(2'-fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-méthyl-4-quinoléinecarboxylique.
- 45 8. Le procédé selon la revendication 1, dans lequel le composé est le sel de sodium ou de potassium de l'acide 2-(1,1'-biphenyl-4-yl)-5-chloro-3-méthyl-4-quinoléinecarboxylique.
9. Le procédé selon la revendication 1, dans lequel le composé est administré en combinaison avec un médicament consistant en un stéroïde.